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(12) Patent:

(11) CA 873873

(54) PREPARATION OF ADAMANTANE-D16

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ABSTRACT

CLAIMS [Show all claims](#)

*** Note: Data on abstracts and claims is shown in the official language in which it was submitted.

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1 This invention is concerned with the preparation
2 of fully deuterated adamantane, that is adamantane-d₁₆ which,
3 itself, is a novel compound.

4 It was found, as one feature of this invention,
5 that adamantane-d₁₆ can be prepared by treating either endo
6 or exo-tricyclo(5.2.1.0.^{2,6})decane with deuterium in the
7 presence of a hydrogenation catalyst at a temperature from
8 about ambient to 300° C. but preferably at about 250° C.
9 The endo or exo-tricyclodecane-d₁₆ (which also are new
10 compounds) formed then can be isomerized to adamantane-d₁₆ by
11 treatment with a reagent capable of accepting electrons
12 known in the profession as Lewis acids. The endo product is
13 initially converted by this process to the exo-tricyclodecane
14 and then to adamantane-d₁₆ and can be carried out either in
15 one step or in two.

16 The catalysts useful for exchange of endo or exo-
17 tricyclodecane are to be found in the class known as hydro-
18 genation catalysts which includes elements of Groups VI, VII
19 and VIII of the periodic table, particularly these consisting
20 of supported Group VIII metal catalysts and more specifically
21 the platinum group which includes ruthenium, rhodium,
22 palladium, osmium, iridium and platinum, although nickel
23 catalysts also are useful. Catalyst supports other than carbon
24 but chosen for their inertness and high surface area also
25 can be employed. Diatomaceous earth (kieselguhr), clay,
26 alumina, and zeolites are some examples of commonly used
27 supports.

28 Either liquid phase exchange or gas phase exchange
29 can be employed for the purpose of deuterating the tricyclo-
30 decane. However, the gas phase exchange generally provides
31 better yields of product of high isotopic and chemical



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1 purity. ~~Is~~omeration preferably is effected over a palladium-
2 supported-on-carbon catalyst at a temperature of 250° C.

3 Preferred catalysts for the isomeration of the
4 endo or exo-tricyclodecane-d₁₆ to adamantane-d₁₆ are aluminum
5 chloride and aluminum bromide although other Lewis acid
6 catalysts, such as FSO₃H-SbF₅, also provide some yield of
7 the desired product. Isomerization can be effected at a
8 temperature ranging from about ambient temperature to 125°C.

9 Alternatively, as another feature of this invention,
10 adamantane-d₁₆ can be prepared by H-D exchange by admixing
11 adamantane with a deuterated hydrocarbon, preferably n-
12 dodecane-d₂₆ or other activated deuterated hydrocarbons
13 from which adamantane can readily be isolated, such as n-
14 decane-d₂₂, n-hexadecane-d₃₄, n-octadecane-d₃₈ and the like
15 in the presence of a hydrogenation catalyst, especially
16 elements of group VIII and more specifically the platinum
17 group which include ruthenium, rhodium, osmium,
18 iridium, platinum and palladium, in a sealed vessel.

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19 The reaction does not need to be carried out under
20 pressure although no disadvantage accrues to the use of a
21 gas such as deuterium to pressurize the reaction vessel to
22 any desired pressure. The vessel must be sealed however to
23 prevent loss of adamantane by sublimation which will occur
24 even at ambient temperature. Adamantane containing de^uterium
25 is recovered by cooling the hydrocarbon solution and filter-
26 ing to remove the solid deuterated adamantane which upon
27 repeated exchange of hydrogen by deuterium according to this
28 process gives adamantane-d₁₆.

29 The H-D exchange advantageously is effected by
30 shaking the reagents in the presence of the hydrogenation
31 catalyst supported on any of the inert materials hereinbefore
32 described at a temperature in the range of ambient to 300°C.

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1 and advantageously at about 100° C.

2 Adamantane-d₁₆ is useful in mass spectral analysis,
3 in nuclear magnetic resonance studies and in radiolysis ex-
4 periments.

5 The use of deuterated compounds as reagents follows
6 from the fact that deuterated compounds undergo the same re-
7 actions as their nondeuterated analogues while modern analyt-
8 ical techniques distinguish between deuterium and hydrogen.
9 Thus the fate of deuterium in reactions with deuterated com-
10 pounds may be directly determined. Adamantane-d₁₆ and its
11 derivatives and exo-tricyclodecane-d₁₆ would be useful for
12 the determination of reaction mechanisms or the detailed
13 description of how reagents are transformed into products
14 and the factors affecting such transformations. Knowledge
15 of reaction mechanisms is in turn helpful in the development
16 of efficient, economical production processes.

17 Another example illustrating the assistance of
18 deuterated compounds in chemical research is that of mass
19 marking. Identification of mass spectral cracking fragments
20 is facilitated by subjecting both a deuterated compound and
21 its undeuterated analogue to mass fragmentation. Fragments
22 from the deuterated compound are shifted one mass unit
23 higher per deuterium atom in the fragment than those from
24 the undeuterated compound. In this way the number of deuterium
25 (hydrogen) atoms in each fragment of the deuterated (undeuterated)
26 compound can be determined. This information greatly
27 simplifies the task of identifying each fragment.

28 Deuterated compounds such as adamantane-d₁₆, its
29 derivatives, and exo-tricyclodecane-d₁₆ also can be used as
30 tracers in the study of separation processes and in com-
31 bustion studies.

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1 Where resistance to decomposition by carbon-hydrogen
2 bond rupture is required, deuterated compounds such as
3 adamantane-d₁₆, its derivatives and exo-tricyclodecane-d₁₆
4 can be employed because as is well known, more energy is
5 required to rupture carbon-deuterium than carbon-hydrogen
6 bonds. For example polymers based on adamantane-d₁₆ can be
7 expected to be less susceptible to oxidative and thermal
8 degradation and thus better withstand extreme environments
9 than nondeuterated analogues.

10 Solid, fully deuterated compounds are often used
11 as targets in neutron diffraction studies. Adamantane-d₁₆
12 is particularly useful for this purpose since large crystals
13 of the compound can be prepared.

14 Deuterated derivatives of adamantane are also use-
15 ful as metabolic tracers to study the metabolism of drugs
16 containing the adamantane nucleus.

17 Adamantane-d₁₆ is also a useful intermediate for
18 preparing deuterated 1-amino adamantane, also known as
19 ~~adamantane~~ adamantine, a product known to have antiviral properties
20 particularly effective against influenza virus and measles
21 virus. The deuterated ~~adamantane~~ adamantine additionally is useful
22 in tracer studies of the activity of this compound against
23 viral agents.

24 Adamantane-d₁₆ can be converted by known procedures
25 to fully deuterated 1-aminoadamantane-d₁₅ by known methods
26 which involve initially treating adamantane-d₁₆ with bromine
27 to provide the 1-bromo derivative. Reaction of the 1-bromo
28 derivative with acetonitrile in the presence of sulfuric
29 acid gives the 1-acetamido derivative which upon hydrolysis
30 with base yields 1-aminoadamantane-d₁₅.

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1 Other commercially useful derivatives of adamantane-
2 d_{16} can be prepared such as 1-adamantanol- d_{15} which can be
3 obtained from the 1-bromoadamantane- d_{15} upon treatment with
4 silver nitrate and water in an organic solvent such as
5 dioxane. Also, 1-adamantane- d_{15} -carboxylic acid can be ob-
6 tained by the reaction of adamantane- d_{16} with a mixture of
7 formic acid and sulfuric acid in tertiary butanol. These
8 latter compounds are commercially useful in the study of
9 separation processes and in combination studies.

10 The following examples will illustrate the novel
11 methods for preparing adamantane- d_{16} . It will be obvious,
12 of course, that modifications in the reaction conditions
13 can be effected without departing from the spirit and scope
14 of this invention.

15 EXAMPLE 1

16 Gas Phase Exchange

17 Step A: Preparation of $\text{exo-tricyclo}[5.2.1.0.2,6]\text{decane-}d_{16}$

18 Exchange is effected by passing deuterium gas at
19 the rate of 9 liters per hour through exo-tricyclodecane in
20 an externally heated 200 ml. flask attached to the bottom of
21 a vertical glass column containing 48 gm. (6%) palladium on
22 carbon, 6-8 mesh, and heated to 250° C. In this way the
23 mixture of deuterium gas and exo-tricyclodecane vapor is
24 passed up through the catalyst bed where exchange is effected
25 and the vapors led into a water cooled condensor arranged so
26 as to permit the return by gravity of condensed exo-tricyclo-
27 decane to the flask at the bottom of the catalyst tower.
28 One hundred grams of exo-tricyclodecane is charged into the
29 bulb at the beginning of the run and 92.8 gm. (or 84 mole %)
30 of substantially pure exo-tricyclodecane-}d_{16} (99.1 atom % D)

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1 obtained after 195 hours of exchange.

2 The deuterium flow rate is not critical. Higher
3 flow rates give faster exchange (less time required to
4 reach 99% D) and lower flow rates give slower exchange.

5 Larger or smaller batch sizes can be used simply
6 by increasing or decreasing the size of the flask used and,
7 if desired, increasing or decreasing the amount of catalyst
8 employed. Larger amounts of exo-tricyclodecane-d₁₆ can also
9 be prepared by connecting two or more runs as described in
10 series or in parallel.

11 Step B: Preparation of adamantane-d₁₆

12 Exo-tricyclo(5.2.1.0.^{2,6})decane-d₁₆ (25 g.) and
13 aluminum chloride (25 g.) are heated at 65° C. for 19 hours
14 with stirring during which period (at the end of 17 hours)
15 deuterium oxide (1 ml.) is added. At the end of 19 hours,
16 the reaction mixture is cooled in ice water, the aluminum
17 chloride destroyed by quenching in a mixture of ice and
18 water (H₂O), the hydrocarbon portion extracted with n-pentane,
19 the pentane solution washed with distilled water, passed
20 through a column of alumina for removal of colored impurities,
21 dried over magnesium sulfate, filtered, and the n-pentane
22 removed by flash evaporation to yield 22.4 g. of a pale
23 yellow liquid-solid slurry. The slurry is cooled to -75° C.
24 and filtered, yielding 9.45 g. of adamantane-d₁₆ (98.9% D)
25 containing 0.3% of unreacted starting material
26 as the only impurity. Sublimation (50° C., 1-2 mm) gives a
27 96% yield (8.40 g.) of adamantane-d₁₆ containing no detectable *chemical*
28 impurities.

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EXAMPLE 2Step A: Preparation of endo-tricyclodecane-d₁₆

25 g. Endo-tricyclo[5.2.1.0^{2,6}]decane put into a glass tube containing 6 g. 6% Pd/C, 6-8 mesh, which is then lowered into a 100° C. oil bath and D₂ gas flow at 100 ml/minute started. Twice a day material solidifying on the cool upper walls of the glass tube is melted and allowed to flow down into the bottom part of the tube. After 25 days of exchange endo-tricyclodecane-d₁₆ is obtained.

Step A': Preparation of endo-tricyclodecane-d₁₆ (98%D)

25 g. Endo-tricyclodecane is dissolved in a slight excess of an appropriate hydrocarbon such as n-dodecane and the resultant solution trickled at a rate of 80 drops per hour over 10 g. 6% Pd/C, 6-8 mesh, heated to 200° C. in the presence of deuterium gas passed through the catalyst bed cocurrent with the liquid feed at a rate of 9 liters per hour. A solution of endo-tricyclodecane (80%D) and n-dodecane (80%D) is obtained. Treating this material twice more under the same conditions gives a solution from which endo-tricyclodecane-d₁₆ (98%D) is isolated in 50% yield by distillation or crystallization, with n-dodecane-d₂₆ (98%D) as a by product.

Exchange is facilitated if a partially or completely deuterated hydrocarbon such as n-dodecane-d₂₆ is used instead of n-dodecane. Valuable deuterated material may be conserved by reusing n-dodecane-d₂₆ in subsequent preparations.

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1 Step A'': Preparation of endo-tricyclo[5.2.1.0^{2,6}]decane-d₁₆

2 A saturated solution of endo-tricyclodecane
3 in a suitable hydrocarbon such as n-dodecane-d₂₆ is shaken
4 with 6% Pd/C catalyst in a Parr hydrogenation bottle heated
5 to 100° C. and connected to a Parr gas reservoir containing
6 30 p.s.i. D₂ gas. Shaking is continued for four (4) days
7 then the catalyst removed by filtration, the solution is
8 cooled and filtered yielding partially deuterated endo-
9 tricyclodecane. Five further exchanges with n-dodecane-d₂₆
10 by the above procedure provides endo-tricyclo[5.2.1.0^{2,6}]-
11 decane-d₁₆ (298%D). A suitable sealed vessel such as a
12 rocking autoclave from which air has been removed may be
13 substituted for the Parr hydrogenation bottle and gas
14 reservoir.

15 Step B: Preparation of adamantane-d₁₆

16 By replacing the exo-tricyclo[5.2.1.0^{2,6}]decane-d₁₆
17 by the thus obtained endo-tricyclodecane-d₁₆ and following
18 substantially the same procedure described in Step B of
19 Example 1 there is obtained adamantane-d₁₆ in substantially
20 the same isotopic purity.

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EXAMPLE 3

Liquid Phase Exchange

3 Step A: Preparation of exo-tricyclo(5.2.1.0.^{2,6})decane

4 Endo-tricyclo(5.2.1.0.^{2,6})decane (197 g.) and
5 aluminum chloride (12 g.) are heated with stirring at 120° C.
6 for three and three quarter hours. The yellow product formed
7 is decanted from the aluminum chloride sludge and vacuum
8 distilled to give exo-tricyclo(5.2.1.0.^{2,6})decane (177 g.,
9 90% yield).

10. Step B: Preparation of *exo*-tricyclo(5.2.1.0^{2,6})decane-d₁₆

11 Exo-tricyclodecane (6.69 g.) is trickled at the
12 rate of 80 drops per hour over 6% Pd/C, 6-8 mesh (5 g.),
13 heated to 147° C. in the presence of deuterium gas passed
14 through the catalyst bed concurrent with the liquid feed at
15 a rate of 4 liters per hour. Deuterated exo-tricyclodecane,
16 4.8 g. (82% D) is obtained. This material is treated twice
17 more under the same conditions to give exo-tricyclodecane-
18 d₁₆ (98% D) in 30% overall yield.

19 A higher liquid to deuterium flow rate gives
20 initial material of lower isotopic purity thus requiring
21 more recycles to reach 98% D whereas, lower liquid/D₂ ratios
22 give material of higher isotopic purity thus requiring fewer
23 recycles to obtain 98% D material.

24 Step C: Preparation of adamantane-d₁₆

25 The exo-tricyclodecane-d₁₆ obtained as described
26 above is converted to adamantane-d₁₆ by the same procedure
27 described in Example 1, Step B.

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EXAMPLE 4H-D Exchange Employing Deuterated Hydrocarbon

Adamantane- d_0 (6.5 g.) and n-dodecane- d_{26} (27 g.) are shaken with 6% palladium on carbon catalyst (20 g.) in a Parr hydrogenation bottle heated to 100° C. which is connected to a Parr gas reservoir containing 30 p.s.i. D_2 gas. After 4 hours additional n-dodecane- d_{26} (20 g.) is added and shaking continued for 4 days. After removal of the catalyst by filtration, the hydrocarbon solution is cooled and filtered yielding 3.0 g. adamantane of 44% D overall. Five further exchanges with n-dodecane- d_{26} by the above procedure provides adamantane- d_{16} (2 98% D).

It should be noted that considerable adamantane remains in solution in n-dodecane when cooled. Maximum yields are obtained by adding more unexchanged adamantane to the deuterated n-dodecane/adamantane solution and exchanging again. This can be done with all the n-dodecane fractions obtained in the six step process thus cutting losses of valuable deuterated material to a minimum.

It was surprisingly found that adamantane- d_{16} can be converted to many useful substituted perdeutero adamantanes by conventional methods without isotope scrambling or dilution. In each case the isotopic purity of the adamantane nucleus of the derivative is identical to that of the adamantane- d_{16} starting material (97.7% D). Material of higher or lower isotopic purity may be used depending on the desired degree of isotopic purity in the adamantane derivative. Adamantane- d_{16} therefore can be employed to prepare derivatives containing the perdeutero adamantane nucleus using standard preparative techniques, and it additionally can similarly be used to prepare completely deuterated derivatives by reacting adamantane- d_{16} with appropriate

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1 deuterated reagents.

2 Preparation of 1-bromo-adamantane-d₁₅

3 To adamantane-d₁₆ (2.0 gm.) in a 100 ml. 3-neck
4 flask fitted with water cooled condenser, dropping funnel,
5 and magnetic stirrer and immersed in an oil bath at 30° C.
6 is added, with stirring, bromine (5 ml.). Stirring is
7 maintained and the bath temperature raised to 105° C. over
8 four and one half hours. The reaction mixture is allowed
9 to cool to room temperature, 20 ml. carbon tetrachloride
10 added and the resulting solution poured into 60 ml. of
11 water in a 250 ml. beaker. The two-phase mixture is
12 cooled in an ice bath and sodium bisulfite added in small
13 portions until the beaker contents are colorless (this
14 serves to destroy residual bromine). The carbon tetrachloride
15 layer is separated, washed with water, the water layer ex-
16 tracted with CCl₄, the CCl₄ layers combined, washed with
17 3 x 20 ml. water and dried over calcium chloride. The CCl₄
18 solution is filtered free of drying agent, CCl₄ removed by
19 flash evaporation and the resultant crude yellow solid
20 (3.23 gm.) recrystallized from hot methanol and sublimed
21 (60° C, 1-2 mm.) to yield 1-bromoadamantane-d₁₅, 2.35 gm.
22 (78 mole%), 98.8% D by n.m.r.

22 Preparation of 1-acetamidoadamantane-d₁₅

23 1-Bromoadamantane-d₁₅ (0.80 gm) and acetonitrile
24 (6 ml.) are placed in a 100 ml. flask fitted with dropping
25 funnel and magnetic stirrer. After the bromoadamantane-d₁₅
26 dissolves, 1.2 ml. concentrated H₂SO₄ is added dropwise
27 with stirring and the reaction mixture stirred for a further
28 15 minutes then allowed to sit overnight (about 18 hours).

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1 The resultant orange solution is poured into 20 ml. distilled
2 water with consequent formation of a white precipitate which
3 is collected by filtration. Neutralization of the filtrate
4 with aqueous sodium hydroxide solution gives a small addi-
5 tional amount of precipitate. The yield is 0.64 gm (89%)
6 of 1-acetamidoadamantane-d₁₅ of 98% D (adamantane nucleus).

7 Preparation of 1-aminoadamantane-d₁₅ (~~adamantadine~~-d₁₅)

8 1-Acetamidoadamantane-d₁₅ (0.50 gm.) is added to
9 a hot solution of crushed sodium hydroxide (1 gm.) in
10 diethylene glycol (10 ml.) and the resulting solution is
11 refluxed for five and one half hours then cooled and poured
12 into 25 ml. of water. The aminoadamantane-d₁₅ so formed is
13 extracted with several portions of ether, the ether layers
14 combined and dried over KOH pellets, the dry ether solution
15 filtered free of drying agent and evaporated to dryness.
16 The resultant solid is sublimed (40° C., 1 mm.) to yield
17 1-aminoadamantane-d₁₅ in 58% yield (0.23 gm.). Further
18 purification is effected by passing dry HCl gas through an
19 ether solution of the compound thus yielding the ether in-
20 soluble 1-aminoadamantane-d₁₅ hydrochloride salt which is
21 isolated by filtration. ~~N.M.R.~~ ^{N.M.R.} shows the adamantane nucleus
22 of this compound to be 98% D.

23 Preparation of 1-adamantanol-d₁₅

24 A mixture of 1-bromoadamantane-d₁₅ (0.617 gm.),
25 dioxane (3 ml.), water (1 ml.), and silver nitrate (0.5 gm.)
26 is refluxed for 3 hours in a 25 ml. flask fitted with a
27 water cooled reflux condenser. The reaction mixture is then
28 cooled, filtered, the filtrate diluted with water and flash

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1 evaporated to dryness. The resultant solid is dried over
2 CaCl_2 (in a dessicator) to yield 0.28 gm. of 1-adamantanol-
3 d_{15} (63 mole %) of 98% D (adamantane nucleus).

4 Preparation of 1-adamantane carboxylic acid- d_{15}

5 Sulfuric acid (17.1 gm.; 95.5%), carbon tetrachloride
6 (3.7 ml.) and adamantane- d_{16} (0.50 gm.) are added to a 100 ml.
7 3-neck flask fitted with a dropping funnel and magnetic
8 stirrer. The reaction flask is lowered into a cooling bath,
9 kept at 17-19° C. then two drops of formic acid (97-100%)
10 added with vigorous stirring followed by the addition over
11 65 minutes of a solution of tertiary butanol (1.1 gm.) in
12 formic acid (2 ml.) with the bath at 20-25° C. Stirring is
13 continued for a further 40 minutes, the reaction mixture
14 poured onto 25 gm. crushed ice, the upper acid layer ex-
15 tracted with 3 x 4 ml. carbon tetrachloride and the combined
16 CCl_4 layers treated with 4 ml. of 15N ammonium hydroxide.
17 The resultant precipitate is collected by filtration, washed
18 with 1 ml. acetone (-75° C.) and then suspended in 10 ml. of
19 water. The free acid is isolated by treatment of the water
20 suspension with 1 ml. of 12N HCl, extraction with chloroform,
21 drying of the chloroform solution over sodium sulphate,
22 filtration to remove drying agent, and flash evaporation to
23 remove solvent. The resultant solid is recrystallized from
24 hot, 3/1, methanol/water to yield 0.32 gm. 1-adamantane- d_{15}
25 carboxylic acid.

26 A small portion of this product is converted to
27 the corresponding methyl ester by treatment with diazomethane.
28 The adamantane nucleus of the methyl ester of 1-adamantane- d_{15}
29 carboxylic acid is shown by mass spectrometry to have an
30 isotopic purity of 98% D.

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Claims:

1 1. A process wherein endo or exo-tricyclo(5.2.1.0.^{2,6})
2 decane, D₂ gas and a hydrogenation catalyst are caused to
3 react at between ambient to about 300° C. to provide the
4 endo or exo-tricyclo(5.2.1.0.^{2,6})decane-d₁₆ which optionally
5 is isomerized at between about ambient and 125° C. in the
6 presence of a Lewis acid to adamantane-d₁₆.

1 2. A process as claimed in Claim 1 wherein
2 deuteration is carried out at a temperature of 250° C. in
3 the presence of palladium on carbon.

1 3. A process as claimed in Claims 1 or 2 wherein
2 isomerization is effected with a Lewis catalyst selected
3 from aluminum chloride, aluminum bromide and FSO₃H-SbF₅.

1 4. Multiple H-D exchanges by combining in a re-
2 action mixture adamantane and a deuterated hydrocarbon in
3 the presence of a hydrogenation catalyst of group VIII
4 elements at between about ambient to about 300° C. to provide
5 adamantane-d₁₆.

1 5. A process as claimed in Claim 4 wherein the
2 reaction mixture is heated at a temperature of about 100° C.

6. Adamantane-d₁₆.

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- 1 7. A perdeutero adamantane derivative selected
- 2 from the group consisting of 1-bromoadamantane- d_{15} , 1-acetamido-
- 3 adamantane- d_{15} , 1-aminoadamantane- d_{15} , 1-adamantanol- d_{15} , and
- 4 1-adamantane carboxylic acid- d_{15} .

8. Exo-tricyclo(5.2.1.0.^{2,6})decane- d_{16} .

9. Endo-tricyclo(5.2.1.0.^{2,6})decane- d_{16} .

*